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PHOSPHOLIPID FORMULATIONS AND THEIR USAGE FOR THE PREPARATION OF LIPOSOMAL MEDICAL AND COSMETIC BATHS

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Phospholipid formulations, characterized in that they contain phosphatidylcholine, and an oil component, an alcohol, a stabilizer, an active ingredient and optionally a processing agent, method for their preparation, and their usage for medical and cosmetic bath preparations.

Description

The object of the invention consists of phospholipid formulations, which contain pharmaceutical or cosmetic active ingredients, and their usage for the preparation of liposomal medical or cosmetic bath preparations.

Bath preparations, particularly conventional oil baths, are very frequently used in medicine and in cosmetics in order to provide the skin with active ingredients acting on a large surface area. They can also be partial baths, such as, for example, foot baths, sitting baths, arm baths or full baths.

The concept of active ingredient is different in this case. Whereas a pharmaceutical active ingredient is suitable for curing skin diseases or influencing them advantageously, to provide relief for colds, or for affecting the circulation and metabolism, a cosmetic active ingredient has another function. A

cosmetic active ingredient, for example, decreases the drying of the hair, it effects a smoothing of the skin, it softens the skin, improves the elasticity of the skin, and protects the skin from the effects of UV radiation.

The most important contents of an oil bath are oil components, an active ingredient as well as one or more emulsifiers, which make it possible to disperse the oil component and the active ingredient, particularly if it is lipophilic in character, in the water.

Typical emulsifiers for oil baths are, for example, ethoxylated or propoxylated fatty alcohols, esters of phosphoric acid, ricinol acid sulfates, alcohol ether sulfates, etc. Depending on the emulsifier proportion, surface spreading (low proportion), milky or clear baths (high proportion) are produced after the mixing of the formulation with the bath water, that is the size of the oil particle of the forming emulsions is influenced by the emulsifier concentration.

Emulsifiers, in addition to their advantage of being capable of dispersing lipophilic substances in water, necessarily have a fat removing effect on the skin, and thus they also bind a large amount of active ingredient, particularly if the latter is lipophilic, in the bath water. Persons skilled in the art are also very well aware of the fact that emulsifiers, as a function of one of their substance parameters, namely the critical micelle concentration, can have an irritating effect on the skin. The higher the critical micelle concentration is, the higher the proportion is of emulsifier molecules that are bound without involvement of micelles, and thus the higher the irritation potential. In addition, the conventional emulsifiers, particularly anionic emulsifiers, effect a strong swelling effect in the corneal layer of the skin (U. Zeidler, Ärtzliche Kosmetologie 19 (3), 208-219 (1989)). Consequently, oil baths are controversial, particularly in the cosmetic field.

Therefore, the goal for an optimal oil bath composition can be defined as a formulation which should contain as much oil component and active ingredient as possible, as little emulsifier as possible, and, in addition, the emulsifier should have as low a fat removing effect as possible, and in addition as low as possible an irritation potential; in addition, the oil component and the active ingredient should be readily available, if possible.

In this context, limits are imposed on the conventional emulsifiers. In addition, for example, in the case of low emulsifier concentrations due to the creaming phenomena due to the oil component, unpleasant fat rims are produced in the bath tub, which are difficult to remove.

The usefulness of medical oil baths has also been

questioned, because the bioavailability of the active ingredients, as indicated above, is very strongly influenced by the emulsifier.

An improvement of the oil bath properties was achieved by a proposal of a mixture made of emulsifier (polyethylene glycol 400 dioleate), isopropyl palmitate, corn oil, lecithin and water (M. Singer, Clinical Medicine 71, 1921-1924 (1964)). However, this mixture too is disadvantageous to the extent that it uses a nonionic emulsifier. Nonionic emulsifiers are known for having the greatest capacity of penetration into the skin in comparison to other emulsifier types (W. Kästner, Seifen, Öle, Fette, Wachse, 116 (1), 3-9 (1990)); in addition, because of its water content, the system contains a preservative (p-hydroxybenzoic acid butyl ester). The allergy triggering effect of preservatives is sufficiently known, and, therefore, precisely in the case of products of the cosmetic and medical type, one seeks to eliminate this risk by the use of preservative-free preparations; however, in this case this is not possible. An additional drawback is the known short shelf life of aqueous lecithin products, because they slowly cleave off fatty acids as a result of hydrolysis of the ester compounds, and thus the properties of the products change. In addition, the described mixture is not protected against autoxidation. However, such protection is very important because lecithin is particularly sensitive due to its high linoleic acid content. This sensitivity can easily be detected even by laymen due to the rancid smell.

The water content has yet another drawback, namely the fact that the oil component and lipophilic active ingredient can only be present in limited amounts, and in addition no hydrolysis-sensitive active ingredients, for example, vitamin A acetate (acne agent), can be included in the formulation. Moreover, the latter active ingredient is also very sensitive to oxidation. The refattening effect of lecithin and of the oil component can still not be completely exploited because of the presence of emulsifiers.

Mixtures of anionic and cationic surfactants with lecithin have also been mentioned (H. Rebmann, Seifen, Öle, Fette, Wachse, 100 (14), 343-346 (1974)). The drawbacks of these formulations are, however, again the presence of emulsifiers, which persons skilled in the art know present an irritation potential and/or influence on the swelling of the corneal layer (see above). All the other drawbacks of the above mentioned mixture could also not be eliminated here, with the exception that vitamin E was described as an additional antioxidant. Here too, persons skilled in the art know that vitamin E has only a limited effect as antioxidant, because it itself is very sensitive to oxygen from the air.

As an additional solution for these problems, it has recently been proposed to use liposomal (oil) baths, in which the

liposomes serve as carriers for the oil and active ingredient components (H. Lautenschläger and J. Röding, Parfümerie und Kosmetik 70 (12), 757-764)).

Liposomes are vesicles having a great variety of structures. Depending on the manufacturing procedure used, one distinguishes between monolamellar, oligolamellar, multilamellar or fused bodies with membrane structure and a diameter of approximately 15-35,000 nm. H. P. Fiedler provides an overview in Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Lexicon of Processing Agents in Pharmacy, Cosmetics and Related Fields], Editio Cantor Publisher, Aulendorf, 1989, pp. 744-746.

In general terminology, liposomes consists of natural, semisynthetic and synthetic phospholipids, where the main component usually consists of phosphatidylcholine. Secondary components are, for example, phosphatidylethanolamine, phosphatidylinosite, phosphatidic acid. A distinction is made between unsaturated (natural), partially hydrated and hydrated phospholipids depending on the fatty acid positions.

As in biological cells, liposomes can store in the interior of the vesicle water soluble substances and in the membranes amphophilic and lipophilic substances (loaded liposomes). Examples for charges in the membranes are vitamin E, retinoid, steroids, lipophilic and amphophilic active ingredients, oils of plant and animal origin.

In particular, lipophilic substances, oils of plant and animal origin, are important in the field of cosmetics for optimizing skin care, especially for the treatment of dry skin. Even in highly unsaturated oils, as used, for example, for the treatment of atopic dermatitis (H. P. Nissen, W. Wehrmann, U. Kroll and H. W. Kreysel, Fat. Sci. Technol. 90 (7), 268-271 (1988)), the distribution and the penetration into the skin are of crucial importance. Liposomes are, therefore, the ideal carrier system with respect to distribution and penetration into the skin.

The liposomes known in the past have, in spite of the mentioned ideal properties, considerable drawbacks:

Liposomes of conventional compositions are considerably more expensive because of the highly purified starting materials that are usually used -- usually highly enriched phosphatidylcholines -- and the complicated manufacturing process, compared to the conventional emulsions with less good properties.

Liposomes of conventional composition have only a low capacity for storage of lipophilic substances. Liposomes made of unsaturated phospholipids can, however, take up approximately 10-30% of their weight of triglycerides; however, this means, for a liposome dispersion with a very high concentration, with 10%

liposome base substance (in the dry substance), a final concentration of 1-3% of triglyceride in the formulation. In comparable oil/water emulsions, in contrast, 10-20% lipophilic components are usually used.

Another harmful drawback with respect to the use of liposomes in bath formulation, is the fact that the finished liposomal bath products contain a very large amount of water (80% and more), and they have to be filled and stored in relatively large packagings (500-1000 mL). These formulations have only limited durability, in spite of the inclusion of preservatives, because the components of the liposomes tend to undergo hydrolysis reactions and they are oxidizable, and thus the composition is changed during storage. Consequently, they can only be stored for limited periods. From today's vantage point, this is not profitable and not practical, and so far it has prevented liposomal bath preparations from becoming economically accepted. The problem can also not be solved by using, for example, freeze dried or spray dried instant liposomes, because they are, on the one hand, very expensive to manufacture, and thus not economical, and, on the other hand, it is precisely the liquid lipophilic components which by their very nature can either not be stored at all or only to a very limited extent. In addition, such formulations take up a particularly large volume and therefore their transport is disadvantageous.

Unexpectedly, an elegant solution or circumvention has been now been found for the above-mentioned problems, consisting in pouring into the bath water, during the preparation of the bath or partial bath, phospholipid formulations, characterized in that they contain phosphatidylcholine (1), an oil component (2), an alcohol (3), a stabilizer (4), an active ingredient (5) and optionally a processing agent (6), where the formation of liposomes with oil and with active ingredients takes place in situ.

The above mentioned main components of the phospholipid formulations (1)-(6) according to the invention are:

(1) Phosphatidylcholine: Products of this type are available commercially under different commercial names, and they are manufactured by the lecithin processors. It is advantageous to use plant phosphatidylcholines, usually obtained from soybeans, or animal phosphatidylcholines, usually obtained from chicken eggs.

(2) Oil component: This component can be made of native oil, (partially) synthetic oil, carboxylic acid esters, liquid wax esters, oily hydrocarbons or mixtures thereof. Native oils are defined as natural oils of plant or animal origin. Plant oils are, for example, sunflower oil, thistle oil, avocado oil, almond oil, soybean oil, ricinus oil, peanut oil, wheat germ oil, carrot oil, apricot core oil, borage oil, primrose oil, hazelnut oil,

palm core oil, sesame seed oil, linseed oil, macadamia nut oil, corn germ oil, beet oil, poppy flour oil, peach core oil, olive oil, walnut oil. Oils of plant origin are, for example, mink oil and fish oil. (Partially) synthetic oils are, primarily, triglycerides whose acid components are made of defined fatty acids, or of mixtures of medium-chain or long-chain fatty acids, for example, caproic acid, capric acid, stearic acid, isostearic acid, palmitic acid, oleic acid, linoleic acid, ricinoleic acid. The synthetic oils also include the silicon oils. Carboxylic acid esters are defined as, for example, isopropyl palmitate, isopropyl myristate, isopropyl stearate, oleyl oleate, myristyl lactate, cetyl lactate, 2-ethylhexyl palmitate, isooctyl stearate, hexyl laurate, dibutyl adipate, 2-octyldecanol, isopropyl linoleate. Liquid waxy esters are contained, for example, in jujube oil. Solid waxy esters can also be used, if they can be separated from the above mentioned liquid oils. Oily hydrocarbons are, for example, paraffin oil, heptamethylnonane.

(3) Alcohol: Alcohol is defined here as preferably ethanol with a content of 90-100%. However, it is also possible to use other straight-chained or branched alcohols or polyalcohols such as, for example, propanol, isopropanol, 1,2-propylene glycol, 1,3-butylene glycol, and glycerin. The use of alcohol has the function of preparing a homogeneous solution during the mixture of the formulation components, but it also has the known skin care characteristic, particularly if 1,2-propylene glycol, 1,3-butylene glycol or glycerin are used.

(4) Stabilizer: Generally the stabilizer used here is urea. It has the function, on the one hand, of producing a quite considerable increase in the resistance to oxidation of the phospholipid formulations according to the invention, and, on the other hand, of guaranteeing the optimal formation of the liposomes during the pouring into the water. In addition, urea is, for a person skilled in the art, a known skin care substance, which is a component of the skin, and whose positive influences on the skin affect, among other systems, the water balance. Typical stabilizers are also monosaccharides such as, for example, glucose, fructose, mannose, galactose, sorbitol, inositol and other saccharides. Naturally, it is also possible to use mixtures of the mentioned stabilizers, if they present advantages.

(5) Active ingredient: The active ingredients can be one or more cosmetically active ingredients, or one or more pharmacologically active ingredients:

Cosmetic active ingredients of the phospholipid formulation according to the invention are fats, vitamins (particularly A, B complex, C, E as well as their usual derivatives such as, for example, vitamin A palmitate, vitamin E acetate), provitamins such as β-carotene, ether oils, self tanning substances such as tyrosines; UV light absorbers such as, for example, urocanic

[sic; possibly urocyanic] acid and esters thereof, skin protection substances such as, for example, ricinoleic acid derivatives, phytosterols, cholesterol, cholesteryl sulfate, squalene, squalane, palmitic acid, stearic acid, isostearic acid. Active ingredients such as panthenol, bisabolol, plant extracts, animal extracts, linoleic acid ester, alpha- and gamma-linolenic acid esters, collagen and elastin hydrolysates and their condensates with fatty acids, glutathion, ceramide, and sphingolipids. Often the above-mentioned oil components (2), such as, for example, oils originating from plants or animals, and waxy esters, also present characteristics of a cosmetic active ingredient because of their composition.

Pharmaceutical active ingredients of the phospholipid formulations according to the invention are retinol and esters thereof, such as chlorhexidine, pruritus reducing substances, nonsteroidal antirheumatics and esters thereof, such as, for example, salicylic acid, salicylic acid methyl ester; inflammation inhibiting agents, blood circulation promoting agents, such as, for example, nicotinic acid benzyl ester; camphor, corticoids, such as hydrocortisone, betamethasone, triamcinolone, dexamethasone, prednisolone; heparin, cytostatics, antihistamines, antiallergic compounds, antibiotics, such as, for example, tetracycline, erythromycin, gentamycin, neomycin; antiparasitic agents, agents that act on the veins, wound treatment agents, astringents, anti-acne agents, antipsoriasis agents, antiseborrheic agents, antisebostatics, keratolytics, scar treatment agents, allantoin, clotrimazole, guajazulen, hexylresorcin, isoprenaline, fumaric acid, fumaric acid ethyl ester, fumaric acid diethyl ester, dithranol, ichthyol, thymol, rosemary oil, panthenol, pantothenic acid, chamomile extract, hamamelis extract, ointment oil, eucalyptus oil, fir needle oil, juniper berry oil, valerian oil, valerian extract, oak bark extract, wheat bran extract, pine needle oil, borneol, menthol, yarrow flower extract, limonen, hayseed extract, whey powder, hop extract, lavender oil, tannin, esculin, escin, salicylamide, mountain pine extract, nicotinic acid methyl ester, nicotinic acid ethyl ester, salicylic acid nicotinate, salicylic acid glycol ester, estradiol, dichlorophene, undecylenic acid, cholecalciferol, placenta extract, thymus extract, benzalkonium chloride, griseofulvin, nystatin, amphotericin B, clotrimazole, miconazole, econazole, tioconazole, ketoconazole, isoconazole, caffeine, ibuprofen, indomethacin, etofenamate, diclofenac, flufenaminic acid, silibinin, silymarin, linoleic acid, alpha-linolenic acid, gamma-linolenic acid, di-homo-gamma-linolenic acid, eicosapentaenoic acid, minoxidil, and superoxide dismutase.

(6) Processing agent: The processing agent is optionally added in the formulation with the phospholipid formulations according to the invention; possible processing agents are, for example, fragrances, perfume oils, antioxidants, such as, for example, ascorbic acid, ascorbic acid palmitate, butyl hydroxytoluene, butyl hydroxyanisole, propyl gallate, vitamin E,

vitamin E acetate, vitamin E palmitate, antioxidant synergists such as, for example, EDTA, 1-hydroxyethane-1,1-diphosphonic acid, citric acid, fumaric acid, uric acid and dyes, as well as mixtures thereof.

Depending on the desired contents of the active ingredients to be used, the contents of the other components of the phospholipid formulations according to the invention are adapted. The contents of the individual components of the phospholipid formulations according to the invention can therefore vary within the following ranges:

Phosphatidylcholine (1)	05.0-70.0 wt%
Oil component (2)	03.0-55.0 wt%
Alcohol (3)	03.0-39.0 wt%
Stabilizer (4)	00.1-07.0 wt%
Active ingredient (5)	00.1-50.0 wt%
Processing agent (optional) (6)	00.1-10.0 wt%

The preferred the contents of the components of the phospholipid formulations according to the invention are as follows:

Phosphatidylcholine (1)	10.0-40.0 wt%
Oil component (2)	20.0-40.0 wt%
Alcohol (3)	20.0-39.0 wt%
Stabilizer (4)	01.0-07.0 wt%
Active ingredient (5)	01.0-10.0 wt%
Processing agent (optional) (6)	00.1-05.0 wt%

Typical compositions of the phospholipid formulations according to the invention are:

(A)

Phosphatidylcholine (1)	10.0 wt%
Oil component (2)	40.0 wt%
Alcohol (3)	39.0 wt%
Stabilizer (4)	01.0 wt%
Active ingredient (5)	09.9 wt%
Processing agent (6)	00.1 wt%
Total	100.0 wt%

(B)

Phosphatidylcholine (1)	40.0 wt%
Oil component (2)	20.0 wt%
Alcohol (3)	20.0 wt%
Stabilizer (4)	01.5 wt%
Active ingredient (5)	08.0 wt%
Processing agent (6)	00.5 wt%
Total	100.0 wt%

(C)

Phosphatidylcholine (1)	26.0 wt%

Oil component (2)	30.9 wt%
Alcohol (3)	35.0 wt%
Stabilizer (4)	07.0 wt%
Active ingredient (5)	01.0 wt%
Processing agent (6)	00.1 wt%
Total	100.0 wt%

(D)

Phosphatidylcholine (1)	21.5 wt%
Oil component (2)	40.0 wt%
Alcohol (3)	20.0 wt%
Stabilizer (4)	03.5 wt%
Active ingredient (5)	10.0 wt%
Processing agent (6)	05.0 wt%
Total	100.0 wt%

(E)

Phosphatidylcholine (1)	05.0 wt%
Oil component (2)	55.0 wt%
Alcohol (3)	20.0 wt%
Stabilizer (4)	19.0 wt%
Active ingredient (5)	01.0 wt%
Processing agent (6)	omitted
Total	100.0 wt%

(F)

Phosphatidylcholine (1)	50.0 wt%
Oil component (2)	40.0 wt%
Alcohol (3)	09.6 wt%
Stabilizer (4)	00.1 wt%
Active ingredient (5)	00.2 wt%
Processing agent (6)	00.1 wt%
Total	100.0 wt%

(G)

Phosphatidylcholine (1)	70.0 wt%
Oil component (2)	03.0 wt%
Alcohol (3)	25.0 wt%
Stabilizer (4)	01.0 wt%
Active ingredient (5)	00.9 wt%
Processing agent (6)	00.1 wt%
Total	100.0 wt%

(H)

Phosphatidylcholine (1)	30.0 wt%
Oil component (2)	06.9 wt%
Alcohol (3)	03.0 wt%
Stabilizer (4)	00.1 wt%
Active ingredient (5)	50.0 wt%
Processing agent (6)	10.0 wt%
Total	100.0 wt%

(G)

Phosphatidylcholine (1)	40.0 wt%
Oil component (2)	03.0 wt%
Alcohol (3)	31.0 wt%
Stabilizer (4)	10.0 wt%
Active ingredient (5)	15.5 wt%
Processing agent (6)	00.5 wt%
Total	100.0 wt%

The phospholipid formulations according to the invention can, in this instance, consist entirely of natural substances or substances identical to natural substances, as illustrated by the following formulation:

Phosphatidylcholine: 90% (soybean) (1)	32.0 wt%
Oil component: Avocado oil (2)	32.0 wt%
Alcohol: Ethanol (3)	32.0 wt%
Stabilizer: Urea (4)	03.2 wt%
Active ingredient: Vitamin E (5)	00.6 wt%
Processing agent: Rose oil (6)	00.2 wt%
Total	100.0 wt%

The method of manufacture of the above listed phospholipid formulations according to the invention is characterized in that a mixture is prepared using consecutively phosphatidylcholine (1), alcohol (3), stabilizer (4), active ingredient (4), processing agent (6) at 20-60°C, preferably 20-40°C, using an anchor stirring system or another conventional stirring system, each time stirring until a solution is obtained; the last step consists of the admixture of oil component (2).

The preparation of the partial or full bath using the phospholipid formulations according to the invention is characterized in that the phospholipid formulations are simply poured into the bath water or mixed with the water as it is poured in; during this process the concentrations can be regulated as desired.

The method for the preparation of a (partial) bath using the phospholipid formulations according to the invention does not present any of the drawbacks mentioned above for conventional bath preparations. This is particularly advantageous for the final user.

The main advantages of the phospholipid formulations according to the invention are:

The phospholipid formulations according to the invention do not differ externally from conventional products, and they can also be used in the same manner, that is the finished liposomal bath preparations are formed simply by pouring of the phospholipid formulations according to the invention into the water. Complicated steps for the preparation of the liposomes present, which are loaded with an oil component and an active

ingredient, are completely eliminated. The phospholipid formulations according to the invention can be prepared by simple mixing or dissolution of the individual components. This can take place at room temperature with a conventional anchor stirring system or another suitable stirring system; the mixing process can, however, also be carried out with the assistance of a heat source, at an elevated temperature of at most 60°C, preferably 20-40°C. The preparation of the liposomal bath preparation is therefore particularly cost advantageous.

Liposomes are only formed in situ when the phospholipid formulations according to the invention are poured into the water. In this process, liposomes are produced which carry particularly high loads of the oil component and the active ingredient. They belong to the so-called lipid-rich liposomal systems.

The phospholipid formulations according to the invention are prepared in an anhydrous process, and they are therefore stable with respect to hydrolysis, and any residual water quantities which are contained by nature in the individual components have no influence on the storage stability. In addition, the phospholipid formulations are not subject to oxidation for year-long periods due to the presence of the stabilizer, which optionally also contains the processing agent, the antioxidants and optionally antioxidant synergists, if the vessel made of a diffusion-proof material such as, for example, glass is closed.

Depending on the dosage of the active ingredients, 10-100 mL of the phospholipid formulations according to the invention are sufficient for a regular full bath.

The phospholipid formulations according to the invention can be prepared exclusively from natural substances, if desired.

The phospholipid formulations according to the invention require no conventional emulsifier for their use. An emulsifier, particularly in large amounts, would precisely have a detrimental effect on the formation of the later liposomal structures, because, in general, emulsifiers destroy the bilayer of the liposomes (H. Hauser, Chimia 39, 252 (1985)).

The liposome base substances, such as phosphatidylcholine, used in the phospholipid formulations according to the invention, are known for penetrating themselves into the skin or through the skin, without having any side effects on the other side, because they are produced by the body itself. In contrast, they have very positive effects on the physiology of the skin, such as, for example, a reduction of transepidermal water loss. Consequently, phosphatidylcholine should be considered a cosmetic active ingredient (H. Lautenschläger, J. Röding and M. Ghyczy, Seifen, Öle, Fette, Wachse, 114 (14), 531-534 (1988)). Thus, today liposomes are considered a source of bilayer materials, which, in

the case of damaged skin, can reestablish damaged bilayers of the corneal layer, an effect which cannot occur with conventional emulsions. An additional advantage of the penetration is the introduction of cosmetic active ingredients into the corneal layer of the skin, which has a storage function, and the transport of pharmacologically active substances into and through the skin. However, in this process, the substances also reach places in the body which can only be reached with difficulty with the usual formulations. This characteristic is important, for example, in partial baths with antimycotically active ingredients against mycoses, particularly ungual mycoses.

It is known that phosphatidylcholine has no defatting effect, because, on the contrary, it partially binds with the keratin of the corneal layer to form complexed compounds. This has the result of a strong refattening effect. This refattening effect is particularly pronounced because the phospholipid formulations according to the invention do not contain a conventional emulsifier, that is one which has a defatting effect by nature.

The use of phosphatidylcholine in the phospholipid formulations according to the invention has the advantage that this compound possesses an extremely low micelle concentration (R. Smith and C. Tanford, J. Mol. Biol. 67, 75-83 (1972)) and, therefore it has no irritating effect on the skin, in comparison to conventional emulsifiers whose critical micelle concentrations are larger by several orders of magnitude.

The durability of the phospholipid formulations according to the invention requires no preservative at all, and therefore the formulations are particularly mild for the skin. Therefore, there is no risk of preservative-caused allergies or sensitivities. Thus, the phospholipid formulations according to the invention are suitable particularly for humans with very sensitive skin, for persons with allergy, psoriasis, atopy, neurodermatitis and other dermatoses such as, for example, ichthyosis. The phospholipid formulations according to the invention can also be used directly for the treatment of these diseases, if corresponding pharmaceutical active ingredients are incorporated into the phospholipid formulations according to the invention. The treatment of sunburns can also be performed very advantageously precisely with strong linoleic and linolenic acid containing phospholipid formulations.

The liposomes and the oil and active ingredient components contained therein, which are produced during the usage of the phospholipid formulations according to the invention, are so finely distributed in the water, that there is no formation of a rim of the oil components as observed with conventional oil baths does not occur. The problems of the fatty rims which remain after the draining of the bath water and which are difficult to remove therefore does not exist in the case of the usage of the

phospholipid formulations according to the invention.

The liposomes which are produced during the usage of the phospholipid formulations according to the invention possess, depending on the composition of the formulation, an average size of 100-2000 nm, that is the size can be controlled by the type and quantity of the individual components.

Depending on the contents of the composition, vesicles with a very large variety of shapes can be produced:

(a) Conventional monolamellar, oligolamellar and multilamellar liposomes with high contents of phosphatidylcholine (1) and low contents of oil component (2) and of active ingredient (5).

(b) So-called propeller liposomes, with comparable contents of phosphatidylcholine (1) and oil component (2) and/or active ingredient (5). Propeller liposomes are characterized by the fact that they consist of aggregates of oil droplets and conventional liposomes.

(c) Chlomicrone-like liposomes, with high contents of oil component (2) and active ingredient (5) and low contents of phosphatidylcholine (1). Chylomicron-like liposomes are characterized by the fact that, if the lamellar liposomal structure is preserved, which consists largely by the phosphatidylcholine (1), they posses a more or less strongly pronounced oily interior phase, which consists of oil component (2) or active ingredient (5). In the extreme case, the interior phase can be completely filled with amphophilic and lipophilic components. These preparations are particularly interesting because they are very cost advantageous as a result of the use of only a small amount of phosphatidylcholine, in the extreme case 5 wt%, and they can be advantageously combined with cosmetically and pharmacologically active albumin hydrolysate condensates as active component (5). As active components it is possible to use, for example, palmitoyl collagen hydrolysate, capryloyl collagen hydrolysate, undecenoyl collagen hydrolysate as well as isolated hydrolysates of casein, keratin and of the hydroxyproline. Naturally, in this regard, it is also possible to use defined pure substances such as, for example, the N-palmitoyl derivatives of glutaminic acid, of arginine, of aspartic acid, of lysine, of serine, and of isoleucine.

What type of liposomal vesicles are formed therefore is determined strongly by the purpose of the usage of the phospholipid formulations according to the invention, because the composition to be selected is a function of the intended use.

Depending on the composition of the phospholipid formulations according to the invention, it is also possible to use mixtures of conventional liposomes, propeller liposomes and

chylomicron-like liposomes.

The manufacture of the phospholipid formulations according to the invention and their use in the case of the utilization of different components is illustrated in the following examples. The phosphatidylcholine used in the examples is enriched at approximately 90%, it originates from soybeans, and it is commercially available under the name of Phospholipon 90. Similar products are also commercially available under other names, for example, Lipoid S 100, Epikuron 200, and Sternlipid PC-90. Naturally, products with low concentration can also be used, if they are compatible with the remaining components. The numbers in brackets before or after the components, from (1) to (6), correspond to the classification given in the description: (1) for phosphatidylcholine, (2) for oil components, (3) for alcohol, (4) for stabilizer, (5) for active ingredient and (6) for processing agent, where, as mentioned in the description, the components in turn can consist of mixtures of individual components.

Example 1
Cosmetic bath

(1) Phosphatidylcholine (90%)	32.0 wt%
(3) Ethanol (96%)	32.0 wt%
(4) Urea	3.2 wt%
(5) Vitamin E	0.6 wt%
(6) Rose oil	0.2 wt%

are stirred with an anchor stirrer and with slight heating (30°C) for approximately 30 min, until a clear yellow solution is produced. The solution is mixed with

(2) Avocado oil (Chem. Laboratorium Richter, CLR 102)	32.0 wt%
	100.0 wt%

The dosage is approximately 50 mL formulation per full bath, where the quantity of water is approximately 150-200 L. The formulation is either poured into the running water, or it is added with manual distribution into the ready water, resulting in a weak turbidity of the water. The water temperature can be any temperature, and, as a rule, it is approximately 35-45°C. The formulation can also be used for partial baths, where accordingly less formulation is used. In the case of particularly strongly acting active components, the dosage is advantageously lowered.

The manufacture and usage of the following examples is analogous to Example 1:

Example 2
Cosmetic bath

Phosphatidylcholine (90%) (1)	10.0 wt%
Sunflower oil (2)	40.0 wt%

1,2-Propylene glycol (3)	39.0 wt%
Urea (4)	01.0 wt%
Bisabolol (5)	09.9 wt%
Vitamin E (6)	00.1 wt%
Total	100.0 wt%

Example 3
Medical bath

Phosphatidylcholine (90%) (1)	40.0 wt%
Jujube oil (2)	20.0 wt%
Ethanol 10 wt%, 1,3-butylene glycol 10 wt% (3)	20.0 wt%
Urea (4)	01.5 wt%
Salicylic acid methyl ester (5)	08.0 wt%
Vitamin E acetate (6)	00.5 wt%
Total	100.0 wt%

Example 4
Medical bath

Phosphoatidylcholine (90%) (1)	26.0 wt%
Soybean oil (2)	30.9 wt%
Ethanol (3)	35.0 wt%
Urea 6.8 wt%, inositol 0.2 wt% (4)	07.0 wt%
Gamma-linolenic acid ethyl ester (5)	01.0 wt%
Vitamin E acetate (6)	00.1 wt%
Total	100.0 wt%

Example 5
Cosmetic bath

Phosphatidylcholine (90%) (1)	21.5 wt%
Wheat germ oil 20 wt%, almond oil 20 wt% (2)	40.0 wt%
1,3-Butylene glycol (3)	20.0 wt%
Urea (4)	03.5 wt%
Squalene 5 wt%, bisabolol 5 wt% (5)	10.0 wt%
Vitamin E acetate 3 wt%, perfume oil 2 wt% (6)	05.0 wt%
Total	100.0 wt%

Example 6
Medical bath

Phosphatidylcholine (90%) (1)	05.0 wt%
Thistle oil 30 wt%, sunflower oil 25 wt% (2)	55.0 wt%
1,2-Propylene glycol (3)	20.0 wt%
Urea (4)	01.0 wt%
Fir needle oil 12 wt%, vitamin E acetate 7 wt% (5)	19.0 wt%
Processing agent (6)	omitted
Total	100.0wt%

Example 7
Cosmetic bath

Phosphatidylcholine (90%) (1)	50.0 wt%
Thistle oil (2)	40.0 wt%
Ethanol (3)	09.6 wt%
Urea (4)	00.1 wt%
Vitamin E palmitate (5)	00.2 wt%
Perfume oil (6)	00.1 wt%
Total	100.0 wt%

Example 8
Medical bath

Phosphatidylcholine (90%) (1)	70.0 wt%
Primrose oil (2)	03.0 wt%
Ethanol (3)	25.0 wt%
Inositol (4)	01.0 wt%
Econazole (5)	00.9 wt%
Vitamin C palmitate (6)	00.1 wt%
Total	100.0 wt%

Example 9
Medical bath

Phosphatidylcholine (90%) (1)	30.0 wt%
Primrose oil (2)	12.9 wt%
Ethanol (3)	03.0 wt%
Urea (4)	00.1 wt%
Rosemary oil (5)	50.0 wt%
Perfume oil 3 wt%, vitamin E acetate 1 wt% (6)	04.0 wt%
Total	100.0 wt%

Example 10
Medical bath

Phosphatidylcholine (90%) (1)	40.0 wt%
Soybean oil (2)	03.0 wt%
Ethanol (3)	31.0 wt%
Urea (4)	10.0 wt%
Ketoconazole (5)	15.5 wt%
Vitamin E acetate (6)	00.5 wt%
Total	100.0 wt%

Patent claims

1. Phospholipid formulations, characterized in that they contain phosphatidylcholine, an oil component, an alcohol, a stabilizer, an active ingredient and optionally processing agent.

2. Phospholipid formulations according to Claim 1, characterized in that the phosphatidylcholine content is 5-70 wt%, preferably 10-40 wt%.

3. Phospholipid formulations according to Claim 1 and 2, characterized in that the phosphatidylcholine used is of plant or animal origin.

4. Phospholipid formulations according to Claims 1-3, characterized in that the oil component content is 3-55 wt%, preferably 20-40 wt%.

5. Phospholipid formulations according to Claims 1-4, characterized in that the oil component is a native oil of plant or animal origin.

6. Phospholipid formulations according to Claims 1-4, characterized in that the oil component is a waxy ester.

7. Phospholipid formulations according to Claims 1-4, characterized in that the oil component is a mineral oil, a liquid synthetic hydrocarbon or silicon oil.

8. Phospholipid formulations according to Claims 1-4, characterized in that the oil component is a neutral oil, that is a synthetic triglyceride, or a skin-compatible ester of an organic carboxylic or dicarboxylic acid.

9. Phospholipid formulations according to Claims 1-8, characterized in that the alcohol content is 3-39 wt%, preferably 20-39 wt%.

10. Phospholipid formulations according to Claims 1-9, characterized in that the alcohol is ethanol, propanol, isopropanol, 1,2-propylene glycol, 1,3-butylene glycol, glycerin or a mixture of these alcohols.

11. Phospholipid formulations according to Claims 1-10, characterized in that the stabilizer content is 0.1-10 wt%, preferably 1-7 wt%.

12. Phospholipid formulations according to Claims 1-11, characterized in that the stabilizer is urea.

13. Phospholipid formulations according to Claims 1-11, characterized in that the stabilizer is a monosaccharide, preferably glucose, fructose, mannose, galactose, sorbitol, or inositol.

14. Phospholipid formulations according to Claims 1-13, characterized in that the active ingredient content is 0.1-50 wt%, preferably 1-10 wt%.

15. Phospholipid formulations according to Claims 1-14, characterized in that the active ingredient consists of one or more cosmetic active ingredients.

16. Phospholipid formulations according to Claims 1-14, characterized in that the active ingredient consists of one or more pharmaceutical active ingredients.

17. Phospholipid formulations according to Claims 1-16, characterized in that the processing agent content of an optional processing agent used in the formulation is 0.1-10 wt%, preferably 0.1-5 wt%.

18. Phospholipid formulations according to Claims 1-17, characterized in that the optional processing agent in the formulation is an antioxidant, an antioxidant synergist, a fragrance or a perfume oil, a dye or a mixture thereof.

19. Method for the preparation of phospholipid formulations according to Claims 1-18, characterized in that the phosphatidylcholine, the alcohol, the stabilizer, the active ingredient, and the processing agent are stirred at 20-60°C, preferably 20-40°C, by means of an anchor stirring device or another conventional stirring device until a solution is obtained, and, in the end, the oil component is admixed.

20. Usage of phospholipid formulations according to Claims 1-18 for the preparation of partial or full liposomal medical baths.

21. Usage of phospholipid formulations according to Claims 1-18 for the preparation of partial or full liposomal cosmetic baths.

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=> s (invert? or revers?)(3a)(micell? or vesicle?)

        248837 INVERT?
        473510 REVERS?
          6618 MICELL?
          5456 VESICLE?
L1         376 (INVERT? OR REVERS?)(3A)(MICELL? OR VESICLE?)

=> s l1 and powder?

        284543 POWDER?
L2         147 L1 AND POWDER?

=> s l2 and 424/450/cclst

          1248 424/450/CCLST
L3          53 L2 AND 424/450/CCLST

=> d 1-53
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1. 5,919,480, Jul. 6, 1999, Liposomal influenza vaccine composition and
method; Eliezer Kedar, et al., **424/450**, 206.1; 436/829 [IMAGE AVAILABLE]

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424/450; 428/402.2 [IMAGE AVAILABLE]

3. 5,877,137, Mar. 2, 1999, Liquid peracid precursor colloidal dispersions oil-core vesicles; Boli Zhou, et al., 510/277; 252/186.25,
186.26, 186.38, 186.39; **424/450**; 510/312, 376, 378 [IMAGE AVAILABLE]

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Alakhov, et al., 424/400, **450**; 514/772.5, 772.6, 772.7 [IMAGE AVAILABLE]

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al., **424/450** [IMAGE AVAILABLE]

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AVAILABLE]

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AVAILABLE]

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424/450; 264/4.6; 424/94.3, 94.6, 196.11, 197.11, 204.1, 234.1, 606,
812; 428/402.2 [IMAGE AVAILABLE]

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=> s (invert? or revers?)(w)(micell? or vesicle?)

        248837 INVERT?
        473510 REVERS?
          6618 MICELL?
          5456 VESICLE?
L4         220 (INVERT? OR REVERS?)(W)(MICELL? OR VESICLE?)

=> s l4 and powder?

        284543 POWDER?
L5          82 L4 AND POWDER?

=> d 1-82
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428/402.2 [IMAGE AVAILABLE]

US PAT NO: 4,578,181 [IMAGE AVAILABLE] L5: 79 of 82

ABSTRACT:
A process of preparing a highly dispersed (colloidal or submicron size)
heterogeneous catalyst for the hydrothermal conversion of heavy oils and
residua is described. The process comprises preparing a **reverse micellar** dispersion by mixing water, an organic solvent, and an ionic
or neutral surfactant to which is added an aqueous solution of a metal
salt. The metal salt is reduced to a colloidal dispersion of the catalyst
in a mixed water-organic liquid phase. The colloidal catalyst is then
blended into resid or heavy oil fractions, and the blend is treated under
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US PAT NO: 4,746,508 [IMAGE AVAILABLE] L5: 76 of 82

ABSTRACT:
Compositions and methods useful for the prevention or treatment of a human or animal disorder or for the regulation of a human or animal physiological condition are provided. The compositions used comprise, in admixture, a biologically-effective amount of a drug specific for the disorder or condition and a biocompatible, water-soluble, amphiphilic steroid, other than a natural bile salt, which is capable of increasing drug permeability of the human or animal body surface across which the drug is to be administered, in an amount effective to increase the permeability of the surface to the drug.

US PAT NO: 5,100,662 [IMAGE AVAILABLE] L5: 70 of 82

ABSTRACT:
The present invention relates to novel liposomes and liposome-like structures (vesicles) comprising an amount of a derivatized sterol either alone or in combination with additional liposome-forming lipids. Sterols such as cholesterol or other lipids, to which numerous charged or neutral groups are attached, may be used to prepare liposomes and liposome-like structures such as micelles, **reverse micelles** and hexagonal phases, suspensions of multilamellar vesicles or small unilamellar vesicles. The novel liposomes of the present invention may be prepared with or without the use of organic solvents. These vesicles may entrap compounds varying in polarity and solubility in water and other solvents. The vesicles of the present invention may function as vaccines after entrapment or association of an immunogen, as adjuvants, either alone or in combination with additional adjuvants, including, for example, Freund's adjuvant (and other oil emulsions), Bortedella Pertussis, aluminum salts and other metal salts and Mycobacterial products (including muramyldipeptides), among others. The present invention relates to novel liposomes and liposome-like structures (vesicles) comprising an amount of a derivatized sterol either alone or
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US PAT NO: 5,230,884 [IMAGE AVAILABLE] L5: 65 of 82

ABSTRACT:
Highly purified and recombinantly produced polypeptides and proteins can be provided to a patient to treat systemic disorders using a metered dose inhaler (MDI). The polypeptides and proteins are solubilized in **reverse micelles** formed from the surfactant in the MDI propellant. By controlling the molar ratio of water to surfactant, the amount of polypeptide or protein solubilized in the **reverse micelles** can be controlled, thereby providing an accurate dosing mechanism. In addition, controlling the molar ratio of water to surfactant also can adjust the size and shape of the **reverse micelles** which will affect the degree and rate of penetration of the lung mucosa for delivery of the drugs to the patient's blood stream.
Proteins which may particularly benefit from the solubilization and systemic delivery process include calcitonin, oxytocin, and insulin.

US PAT NO: 5,770,559 [IMAGE AVAILABLE] L5: 22 of 82

ABSTRACT:
Provided is a method for preparing a true, homogeneous solution of a pharmaceutical substance dissolved in an organic solvent in which the pharmaceutical substance is not normally soluble. Solubilization is obtained by forming a hydrophobic ion pair complex involving the pharmaceutical substance and an amphiphilic material. The resulting organic solution may be further processed to prepare pharmaceutical **powders**. A biodegradable polymer may be co-dissolved with the pharmaceutical substance and the amphiphilic material and may be incorporated into a pharmaceutical **powder**. A preferred method for preparing pharmaceutical **powders** is to subject the organic solution to gas antisolvent precipitation using a supercritical gas antisolvent such as carbon dioxide. Also provided is a method for making hollow particles having a fiber-like shape which would provide enhanced retention time in the stomach if ingested by a human or animal host.

US PAT NO: 5,807,573 [IMAGE AVAILABLE] L5: 17 of 82

ABSTRACT:

A biologically active composition containing (a) a diacyl glycerol, (b) a phospholipid and, optionally, (c) a polar liquid in such proportions that they together form an L2-phase or a cubic liquid crystalline phase, in which a biologically active material is dissolved or dispersed. A method for preparing the composition by mixing (a), (b) and, optionally, (c) for forming an L2-phase or a cubic liquid crystalline phase, the biologically active material being added before, during or after the formation of said phase. Use of the L2-phase or the cubic liquid crystalline phase for encapsulating a biologically active material for obtaining a preparation is provided, which yields a controlled release of t